REMARKS

Claim Status

Claims 35-68 are pending in the application. Claims 54-68 were withdrawn by the Examiner as being drawn to a non-elected invention. Claims 35, 36, 41, 54, 55, 58, 59, 63 and 68 have been amended. Claim 69 is new.

Claim Amendments

Claim 35 has been amended to more clearly indicate that the isolated aldonic acid ester is of a polysaccharide, starch or a hydroxyalkyl derivatized starch. Support for this amendment appears in the English Translation of the Specification at page 7, lines 5-9.

Claim 36 has been amended to delete "optionally substituted".

Claim 41 has been amended to more clearly indicate that the starch fraction is derivatized to from a hydroxyethyl starch fraction.

Claim 69 is new and finds support in the English Translation of the Specification at page 7, lines 5-9.

Withdrawn Claims 54, 55, 58, 59, 63 and 68 have been amended to be consistent with the amendment made to base Claim 35 and to delete "optionally substituted". These claims are being amended to preserve the opportunity for rejoinder, upon allowance of product Claims 35-53.

Rejection of Claims 35-53 under 35 U.S.C. §112, Second Paragraph

Claims 35-53 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner stated, that the term "optionally substituted polysaccharide" renders claims 35, 36 and 41 indefinite.

Claims 35-36 and 41 have been amended by replacing the term "optionally substituted polysaccharides" with the phrase "a polysaccharide, starch or a hydroxyalkyl derivatized starch". Such amendment is clearly supported in the specification and particularly defines the substituted polysaccharide to be a hydroxyalkyl derivatized starch. Applicants submit that Claims 35-36 and 41, as amended, are definite. Reconsideration and withdrawal of the rejection are respectfully requested.

Withdrawn Claims 54, 55, 58, 59, 63 and 68 have been amended to be consistent with the amendment made to base Claim 35. These claims are being amended to preserve the opportunity for rejoinder, upon allowance of product Claims 35-53.

Rejection of Claims 35-38 and 41-53 under 35 U.S.C. §103(a)

Claims 35-38, 41-53 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Sommermeyer *et al.*, an International Application publication WO 2002/080979 (hereinafter "Sommermeyer"), the U.S. National stage of which is published as U.S. Publication No. US 2005/0063943, in view of chapter entitled "Zero-Length Cross-linkers" by G. T. Hermanson, Bioconjugate Techinques, page 170-180, 1999 (hereinafter, "Hermanson"), as evidenced by Marder *et al.*, and as evidenced by the "WHO Food Additives Series No. 5."

The Examiner stated that it would have been obvious to one of ordinary skill in the art to combine teachings of Sommermeyer, concerning a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyl starch is coupled to the active ingredient either directly or via a linker using EDC, with the teaching of Hermanson, regarding the use of EDC/sulfo-N-hydroxysuccinimide (sulfo-NHS) in a conjugation reaction as an alternative to EDC.

As stated by the Examiner (the paragraph 2 on page 6 in the Office Action) Sommermeyer discloses in Example 2 (paragraph [0147]) a compound, which is a product of a coupling reaction between hydroxyethyl starch (HES) oxidized at the reducing end and Human Serum Albumin (HSA) protein. The reaction is proceeding in water, in the presence of ethyldimethyl-aminopropyl-carbodiimide (EDC). The Examiner stated that this coupling reaction and its product are further exemplified in Table 2 (page 11 of Sommermeyer). The Examiner asserts that an ester, as defined in the instant application on page 9 of the instant specification, is formed when an acid (oxidized hydroxyethyl starch (ox-HES)) is reacted with EDC in the presence of 1-hydroxy-1H-benzotriazolhydrate (1-HOBt). The Examiner is citing Marder et al., "Industrial application of coupling reagents in peptides", Chimica Oggi (Chemistry Today), 2003 (hereinafter, "Marder"), in support of his assertion.

The reaction of HES, oxidised at the reducing end, with EDC and HOBt according to example 2 of Sommermeyer *et al.* (US 2005/0063943) was performed in an aqueous solution [0147]. It is not disclosed whether this activation leads to an HES-ester with HOBt or not, but it is well known that such stable esters are only obtainable in anhydrous solvents. Under

conditions disclosed in example 2, a person skilled in the art would expect the formation of 0-acylisourea which will immediately react with the protein.

Hence, in contrast to the conditions used in Sommermeyer *et al.*, the esterification of the polysaccharide with the HOBt in the present application takes place in an anhydrous aprotic solvent (p. 10, last para.).

According to the Examiner, a person skilled in the art would combine the teaching of the cited documents and expect, as described by Hermanson *et al*, that the reaction of the sulfo-NHS with the EDC-activated complex would increase the half-life of the activated group to some hours and would increase the yield of the coupling-reaction dramatically.

HOBt is as an activator on a par with hydroxysuccinimide or sulfohydroxysuccinimide, as disclosed in "Chemical Approaches to the Synthesis of Peptides and Protein", Paul Lloyd-Williams *et al.*, CRC-Press (1997), page 48-53 (attached as Exhibit A and cited on the accompanying Information Disclosure Statement as reference C10).

Actually it would not be obvious to a person skilled in the art that the reaction of the sulfo-NHS with the EDC-activated complex would increase the yield of the coupling-reaction dramatically. This is quite the contrary to the teaching of Hermanson *et al.* From Example 2 of Sommermeyer *et al.*, also cited by the Examiner, it is shown that the activation with HOBt (coupling C, table 2) reduces the yield, possibly by encouraging secondary reaction.

Therefore, a person skilled in the art would not combine the teaching of Sommermeyer *et al.* with the teaching of Hermanson *et al*, since it is already known from Sommermeyer *et al.* that activation with HOBt reduces the yield. Thus, Sommermeyer *et al.* teaches away from using HOBt as an activator.

Hence also the isolation of an intermediate product is also not obvious.

According to the publication of Hermanson *et al.* (see reference on page 170) OH-groups can react with the activated acids. See also example 6 of WO/02/080979 (Sommermeyer *et al.*). In these experiments it was determined whether secondary reactions in the form of self-condensation of HES with oxidized reducing end groups occur. It was shown that in aqueous solution the mixture of HES with oxidized reducing end groups, HOBt and EDC does not lead to the self-condensation of HES, which would be expected when the formed o-acylisourea or the reactive ester with HOBt would react intermolecular with the OH-groups of the HES-Acid.

Thus, the present invention surprisingly solves the problem of the present application. *Inter alia* the problem associated with the use of carbodiimides has been overcome, that

carbodiimides cause very frequently inter- or intramolecular crosslinking reactions of the proteins as side effects. In the case of compound containing phosphate groups, such as nucleic acids, the coupling is often impossible because the phosphate groups may likewise react with EDC (page 2, line 7-14 of the present application).

Based on the above arguments it would not have been obvious that the reaction in anhydrous aprotic solvents leads to the desired reaction products, based on the cited prior art documents. Therefore, Applicants submit that independent Claim 35, as amended, and Claims 36-38 and 43-46, dependent thereon, are non-obvious over the cited art. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) are respectfully requested.

Rejection of Claims 39 and 40 under 35 U.S.C. §103(a)

Claims 39 and 40 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Sommermeyer, in view of chapter entitled "Zero-Length Cross-linkers" by G. T. Hermanson, Bioconjugate Techinques, page 170-180, 1999 (hereinafter, "Hermanson"), as evidenced by Marder *et al.*, and as evidenced by the "WHO Food Additives Series No. 5," as applied to Claims 35-38, 41-53, further in view of Gunja *et al.*, in view of Mau *et al.*

The Examiner stated that it would have been obvious to one of ordinary skill in the art to choose an amylopectin, with the appropriate degree of branching to yield a product with the desired gelling properties, for conjugation to a drug.

Applicant's submit that independent Claim 35, as amended, is novel and non-obvious over Sommermeyer, for the reasons discussed in the preceding section of this reply. Claims 39 and 40 depend directly or indirectly on Claim 35, and therefore, are also novel and non-obvious over Sommermeyer. The secondary references do not remedy the deficiencies of Sommermeyer. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) are respectfully requested.

Information Disclosure Statement

An Information Disclosure Statement (IDS) was filed on June 1, 2005. Applicant's respectfully request references B1, B2 and B3 be reconsidered as the translation requirement was complied with as the International Search Report was filed concurrently. A Supplemental Information Disclosure Statement is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Alice O. Carroll

Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Date: February 4, 2010